

THE DETECTION OF GENETIC CARRIERS

With the conquest of the infectious and contagious diseases, medical attention has been increasingly directed toward constitutional conditions, in which the role of genetic factors is often evident. A working knowledge of genetics enables the physician to provide early diagnosis and prevention or treatment of latent hereditary disease, to arrive at the correct diagnosis of an atypical case by recognizing the frank form in other family members, and to furnish genetic prognosis to families.

An individual who possesses the potentialities of transmitting inherited disease, and who may himself become severely affected later in life, will often show some slight abnormality which allows the alert physician to prevent or ameliorate the full-blown disease. Such a mild or unexpressed case is termed a genetic carrier, by analogy with the asymptomatic carrier of infectious disease. Genetic carriers include: (1) an individual with the genetic potentialities for developing a disease of late onset; (2) an individual showing only minor effects of a disease of variable manifestation; (3) the heterozygote for an incompletely recessive gene. Sometimes the carrier state is recognized before the genetic basis is understood, but this does not interfere with effective use of carrier information in prevention and treatment of the disease.

There are so many diseases in which a carrier state can sometimes be recognised, the accuracy of carrier detection is so variable, and our ability to diagnose carriers is increasing so rapidly, that it is not feasible to provide a simple list of diseases in which carriers can be detected. Some useful references are given below, and others may be found in recent issues of the major medical journals. A few examples of the use of carrier detection in prevention and therapy will now be given. These are illustrations, and represent only a small fraction of the diseases in which carrier detection is possible and useful.

Hereditary spherocytosis. Carriers for this dominant gene present a range of symptoms, from increased erythrocyte fragility to marked spherocytosis and severe anemia. They are subject to grave aplastic crises, during which erythropoiesis fails. The outcome is often fatal. The majority of untreated cases develop gallstones. Fortunately, splenectomy completely removes the risk of aplastic crises, anemia, and gallstones, and preventive splenectomy is recommended in all cases that can be diagnosed. It would not be feasible to apply to all persons in the population the special hematological tests required for diagnosis, but such tests should be applied to all close relatives. On the average, half the children of carriers are also affected, often severely. Many, but less than half, of the siblings of patients are affected, since elimination of the gene by aplastic crises is balanced by mutation, and some cases are sporadic. However, half the children of sporadic cases are also affected. Because splenectomy cures the disease, and splenectomized patients survive the reproductive period, the frequency of the gene must be increasing.

Phenylketonuria. Homozygotes for this incompletely recessive gene are marked by phenylpyruvic acid in the urine, abnormally high phenylalanine levels in serum, gross mental defect, and characteristic neurologic and dermatologic findings. Urine specimens of these cases usually give a positive ferric chloride test, which provides a simple and precise diagnosis. The basis of the defect has been shown to be the absence of an enzyme which converts phenylalanine to tyrosine. Heterozygotes are clinically normal, but usually have elevated serum phenylalanine levels. When a test dose of phenylalanine is administered, heterozygotes show abnormally high serum ratios of phenylalanine to tyrosine. Both parents of a phenylketonuric patient give this response; on the average, one half of the siblings are also heterozygotes, and one quarter are mentally deficient phenylketonurics. About one per cent of the general population are heterozygous carriers. It is not known whether the mentality of carriers is in any way abnormal.

The development of severe mental defect in homozygotes can be alleviated, perhaps prevented, if in early infancy they are placed on a special diet low in phenylalanine. This treatment seems to be much less effective if it is not started in infancy. At that age mental development cannot be accurately measured, but the biochemical abnormality can be detected. By prompt treatment of homozygous younger siblings of patients with phenylketonuria, many of the effects of the disease can be reversed.

Galactosemia. This is an inborn error of metabolism, apparently due to an incompletely recessive gene. Homozygotes lack the enzyme P-gal-transferase which converts galactose-1-phosphate to glucose-1-phosphate. Untreated cases develop feeding difficulties, hepatomegaly, cataract and mental deficiency, and usually die in infancy. Therapy consists in removing all lactose and galactose from the diet. With early treatment, development is essentially normal. If treatment is delayed, the cataracts and liver damage are irreversible. About half the heterozygotes can be detected by a galactose tolerance test, while homozygotes can invariably be recognized by the absence of transferase in their erythrocytes. Younger siblings of patients with galactosemia should be tested at birth, and treatment begun immediately for the 25% who are affected.

Gout. In this disease the serum uric acid level is elevated, and crystals of sodium urate may be deposited in the urogenital tract and many body tissues, causing renal damage and recurrent severe arthritic attacks. Patients are heterozygous for a gene which produces hyperuricemia, but only about 10% of males with the gene, and even fewer females, develop clinical gout. This sex difference is in part due to the fact that women have lower normal blood levels of uric acid than men. Hyperuricemia is found in half the parents and sibs of patients with gout. Onset of the disease in hyperuricemic males can be prevented or retarded by generous fluid intake and restriction of purines in the diet. Once the disease is manifest, development of chronic

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tophaceous gout can be checked by administration of uricosurics like benemid. If treatment is delayed, renal impairment and destruction of joints by gouty tophi may be severe.

Pernicious anemia. Because of a genetically determined defect in the stomach lining, persons with this disease develop a severe anemia, preceded and accompanied by achlorhydria. The exact genetic basis of the condition is not known, but achlorhydria is common in relatives, and a family history of pernicious anemia is often obtained. Routine administration of vitamin B₁₂ will prevent the disease in the achlorhydric relatives.

Genetic carriers in diagnosis. Sometimes the family history leads to a correct diagnosis that otherwise would be missed or delayed. An atypical case of anhidrotic ectodermal dysplasia was made worse by thyroid therapy because of a misdiagnosis as hypothyroidism, but a study of the family history led to the correct diagnosis. Familial periodic paralysis resembles other conditions clinically, but differs in that it responds to potassium chloride in some kindred. In other kindred, similar conditions show no response. A patient with the disease can always be successfully treated, if potassium chloride is effective for a relative with the same disease. A major operation for tic douloureux was cancelled after reconsideration of a family history of diabetes, which suggested the correct diagnosis of diabetic neuritis. In another instance, when the diagnosis appeared to lie between gastric ulcer, Banti's disease, and cirrhosis of the liver with esophageal varices, the attending physician correctly diagnosed and excised a telangiectatic spot in the gastric mucosa, because he knew that the patient's father had the dominant disease telangiectasia. Patients with muscular dystrophy have been prematurely confined to wheelchairs through delayed diagnosis and treatment, in spite of a clear family history. Many other examples could be cited, in which consideration of the family history may lead to early diagnosis and more effective treatment.

References

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